



## **Eschar removal by bromelain based enzymatic debridement (Nexobrid®) in burns: European consensus guidelines update**

Hirche, Christoph ; Kreken Almeland, Stian ; Dheansa, Baljit ; Fuchs, Paul ; Governa, Maurizio ;  
Hoeksema, Henk ; Korzeniowski, Tomasz ; Lumenta, David B ; Marinescu, Silviu ; Martinez-Mendez,  
José Ramón ; Plock, Jan A ; Sander, Frank ; Ziegler, Benjamin ; Kneser, Ulrich

**Abstract:** INTRODUCTION Bromelain-based Enzymatic Debridement has been introduced as an additional concept to the burn surgeon's armamentarium and is best indicated for mid-to deep dermal burns with mixed patterns. Increasing evidence has been published focusing on special regions and settings as well as on limitations of Enzymatic Debridement to improve patient care. To better guide Enzymatic Debridement in view of the increasing experience, there is a need to update the formerly published consensus guidelines with user-orientated recommendations, which were last produced in 2017. METHODS A multi-professional expert panel of plastic surgeons and burn care specialists from twelve European centers was convened, to assist in developing current recommendations for best practices with use of Enzymatic Debridement. Consensus statements were based on peer-reviewed publications and clinical relevance, and topics for re-evaluation and refinement were derived from the formerly published European guidelines. For consensus agreement, the methodology employed was an agreement algorithm based on a modification of the Willy and Stellar method. For this study on Enzymatic Debridement, consensus was considered when there was at least 80 % agreement to each statement. RESULTS The updated consensus guidelines from 2019 refer to the clinical experience and practice patterns of 1232 summarized patient cases treated by the panelists with ED in Europe (2017: 500 cases), reflecting the impact of the published recommendations. Forty-three statements were formulated, addressing the following topics: indications, pain management and anesthesia, large surface treatment, timing of application for various indications, preparation and application, post-interventional wound management, skin grafting, outcome, scar and revision management, cost-effectiveness, patient's perspective, logistic aspects and training strategies. The degree of consensus was remarkably high, with consensus in 42 out of 43 statements (97.7%). A classification with regard to timing of application for Enzymatic Debridement was introduced, discriminating immediate/very early ( 12 h), early (12-72 h) or delayed (>72 h) treatment. All further recommendations are addressed in the publication. CONCLUSIONS The updated guidelines in this publication represent further refinement of the recommended indication, application and post-interventional management for the use of ED. The published statements contain detailed, user-orientated recommendations aiming to align current and future users and prevent pitfalls, e.g. for the successful implementation of ED in further countries like the USA. The significance of this work is reflected by the magnitude of patient experience behind it, larger than the total number of patients treated in all published ED clinical trials.

DOI: <https://doi.org/10.1016/j.burns.2020.03.002>



The following work is licensed under a Creative Commons: Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.

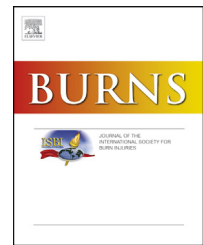
Originally published at:

Hirche, Christoph; Kreken Almeland, Stian; Dheansa, Baljit; Fuchs, Paul; Governa, Maurizio; Hoeksema, Henk; Korzeniowski, Tomasz; Lumenta, David B; Marinescu, Silviu; Martinez-Mendez, José Ramón; Plock, Jan A; Sander, Frank; Ziegler, Benjamin; Kneser, Ulrich (2020). Eschar removal by bromelain based enzymatic debridement (Nexobrid®) in burns: European consensus guidelines update. *Burns*, 46(4):782-796.

DOI: <https://doi.org/10.1016/j.burns.2020.03.002>

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.elsevier.com/locate/burns](http://www.elsevier.com/locate/burns)

# Eschar removal by bromelain based enzymatic debridement (Nexobrid®) in burns: European consensus guidelines update

Christoph Hirche<sup>a,\*</sup>, Stian Kreken Almeland<sup>b</sup>, Baljit Dheansa<sup>c</sup>,  
Paul Fuchs<sup>d</sup>, Maurizio Governa<sup>e</sup>, Henk Hoeksema<sup>f</sup>,  
Tomasz Korzeniowski<sup>g</sup>, David B. Lumenta<sup>h</sup>, Silviu Marinescu<sup>i</sup>,  
José Ramón Martínez-Mendez<sup>j</sup>, Jan A. Plock<sup>k</sup>, Frank Sander<sup>l</sup>,  
Benjamin Ziegler<sup>a</sup>, Ulrich Kneser<sup>a</sup>

<sup>a</sup> BG Trauma Center, Hand-, Plastic and Reconstructive Surgery, Microsurgery, Burn Center, University of Heidelberg, Ludwigshafen, Germany

<sup>b</sup> Department of Plastic and Reconstructive Surgery, Haukeland University Hospital, Faculty of Medicine, University of Bergen, Bergen, Norway

<sup>c</sup> Queen Victoria Hospital NHS Foundation Trust, East Grinstead, United Kingdom

<sup>d</sup> Department of Plastic Surgery, Hand Surgery, Burn Center, University of Witten/Herdecke, Cologne-Merheim Medical Center (CMMC), Cologne, Germany

<sup>e</sup> Division of Plastic and Reconstructive Surgery and Burns Centre, University Hospital of Verona - A.O.U.I., Verona, Italy

<sup>f</sup> Burn Unit, Department of Plastic and Reconstructive Surgery, Ghent University Hospital, Ghent, Belgium

<sup>g</sup> East Centre of Burns Treatment and Reconstructive Surgery, Łęczna, Poland

<sup>h</sup> Division of Plastic, Aesthetic and Reconstructive Surgery, Department of Surgery, Medical University of Graz, Graz, Austria

<sup>i</sup> Department of Plastic and Reconstructive Surgery, "Bagdasar-Arseni" Clinical Emergency Hospital, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

<sup>j</sup> Burn Unit, Hospital Universitario La Paz, Madrid, Spain

<sup>k</sup> Division of Plastic Surgery and Hand Surgery, Burn Center, University Hospital Zurich, Zurich, Switzerland

<sup>l</sup> Burn Center with Plastic Surgery, Unfallkrankenhaus Berlin, Berlin, Germany

## ARTICLE INFO

### Article history:

Accepted 1 March 2020

### Keywords:

Burn  
Enzymatic debridement  
Nexobrid  
Consensus  
Eschar removal

## ABSTRACT

**Introduction:** Bromelain-based Enzymatic Debridement has been introduced as an additional concept to the burn surgeon's armamentarium and is best indicated for mid-to deep dermal burns with mixed patterns. Increasing evidence has been published focusing on special regions and settings as well as on limitations of Enzymatic Debridement to improve patient care. To better guide Enzymatic Debridement in view of the increasing experience, there is a need to update the formerly published consensus guidelines with user-orientated recommendations, which were last produced in 2017.

**Methods:** A multi-professional expert panel of plastic surgeons and burn care specialists from twelve European centers was convened, to assist in developing current recommendations for best practices with use of Enzymatic Debridement. Consensus statements were based on peer-reviewed publications and clinical relevance, and topics for re-evaluation and

\* Corresponding author at: BG Trauma Center Ludwigshafen, Department of Hand-, Plastic and Reconstructive Surgery, Microsurgery, Burn Center, University of Heidelberg, Ludwig Guttman Str. 13, 67071 Ludwigshafen, Germany.

E-mail address: [christoph.hirche@bgu-ludwigshafen.de](mailto:christoph.hirche@bgu-ludwigshafen.de) (C. Hirche).

<https://doi.org/10.1016/j.burns.2020.03.002>

0305-4179/© 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

refinement were derived from the formerly published European guidelines. For consensus agreement, the methodology employed was an agreement algorithm based on a modification of the Willy and Stellar method. For this study on Enzymatic Debridement, consensus was considered when there was at least 80 % agreement to each statement.

**Results:** The updated consensus guidelines from 2019 refer to the clinical experience and practice patterns of 1232 summarized patient cases treated by the panelists with ED in Europe (2017: 500 cases), reflecting the impact of the published recommendations. Forty-three statements were formulated, addressing the following topics: indications, pain management and anesthesia, large surface treatment, timing of application for various indications, preparation and application, post-interventional wound management, skin grafting, outcome, scar and revision management, cost-effectiveness, patients perspective, logistic aspects and training strategies. The degree of consensus was remarkably high, with consensus in 42 out of 43 statements (97.7%). A classification with regard to timing of application for Enzymatic Debridement was introduced, discriminating immediate/very early ( $\leq 12$  h), early (12–72 h) or delayed ( $> 72$  h) treatment. All further recommendations are addressed in the publication.

**Conclusions:** The updated guidelines in this publication represent further refinement of the recommended indication, application and post-interventional management for the use of ED. The published statements contain detailed, user-orientated recommendations aiming to align current and future users and prevent pitfalls, e.g. for the successful implementation of ED in further countries like the USA. The significance of this work is reflected by the magnitude of patient experience behind it, larger than the total number of patients treated in all published ED clinical trials.

© 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Since its approval in Europe in 2013, Bromelain-based Enzymatic Debridement with Nexobrid<sup>®</sup> has become a reliable and useful alternative to operative eschar removal, which has been found to be most beneficial in mid- to deep dermal burns and mixed depth patterns. There is a continuously growing number of burn centers successfully treating an increasing number of burn patients, with Enzymatic Debridement with beneficial outcome. Several studies have addressed the selective approach and advantages of Enzymatic Debridement, which may reduce procedural blood loss, the need for autologous skin grafting and the number of wounds with further surgical excision by preserving more viable dermis compared to the standard of care (SOC) [1]. Additionally, Enzymatic Debridement has the advantage of reducing the rate of burn wound infection and the length of hospital stay compared to SOC [2].

In a first European consensus expert panel meeting on Enzymatic Debridement with Nexobrid<sup>®</sup> in 2017, the experience of treating more than 500 adult and pediatric patients was summarized by addressing relevant issues as a preliminary guideline with user-oriented recommendations for a successful implementation [3]. Sixty-eight consensus statements were provided, with a remarkably high degree of 88.2 % consensus for all statements [3].

Within the last 5 years, increasing evidence on Enzymatic Debridement has been published with a focus on special regions and settings. Likewise, its limitations have been discussed in order to increase success rates and acceptability in view of improved patient care and outcome.

Hot topics on enzymatic debridement that have been addressed were the special issues of treating burned hands [4–9] as well as burns to the face [10] and genitals [11], with most published studies and patients on hand burns.

Immediate application of Enzymatic Debridement in circumferential burns to the extremity was investigated by Fischer et al. who showed its effectiveness and safety for the prevention of burn-induced compartment syndrome in clinical practice, reducing the need and burden of surgical escharotomy [12].

Another important issue, the “quality” of enzymatic debridement was examined taking biopsies harvested from partial thickness burn wounds, before and after enzymatic treatment, with additional histological assessment [13]. The authors demonstrated that partially damaged dermis was always spared by enzymatic debridement, but showed some “homogenization” characteristics and only few vital skin adnexal structures. They concluded that this dermal portion could desiccate if mismanaged as a trigger for neo-eschar or the well-known pseudo-eschar after enzymatic debridement with Nexobrid<sup>®</sup> [13].

As a consequence of successful clinical application, cost-efficacy analyses and associated implementation strategies for Nexobrid<sup>®</sup> based on national models and calculations due to different reimbursement modalities have become another relevant focus of enzymatic debridement in burns [14,15]. The treatment of diabetic foot burns has been demonstrated as a limitation due to deepening and unfavorable outcome in a case series [16]. Delayed application after the thermal injury was addressed in view of logistical reasons and patient stability. With special burn wound preparations prior to Enzymatic Debridement, delayed application has been demonstrated as

feasible [17]. Some case reports addressed fractional and delayed Enzymatic Debridement in large burn surfaces [18] and the relevance of coagulation abnormalities [19] — issues that all should be newly reevaluated in view of this new modality.

In order to update the role and advantages of Bromelain-based Enzymatic Debridement since the first European consensus meeting on Enzymatic Debridement in 2017, a 2<sup>nd</sup> European consensus meeting was scheduled in order to re-evaluate the former consensus statements and focus on new relevant issues.

## 2. Methods

During the first European consensus meeting in 2017 [3], consensus statements on Enzymatic Debridement for eschar removal in burns were formulated by a multistep process. In brief, a systematic literature review of the recent literature (2013–2018) including the publication of the first European consensus meeting was used as a basis for pre-formulated statements by CH, UK and BZ addressing all relevant topics. These statements were sent to all panelists in advance and were the basis for panel discussions. Due to the limited number of publications and the novelty of the treatment modality of enzymatic debridement in burns, systematic consensus measures (e.g., Delphi method) were not applied, and a modified consensus process was implemented.

### 2.1. Panelists

European expert panelists were selected by the first and senior author (CH and UK) based on the following criteria: clinical experience and prior publications on Enzymatic Debridement with Nexobrid<sup>®</sup>, general expertise and reputation in burn treatment, and role as key opinion leader. Selection of panelists was limited to Europe due to the medical approval of Nexobrid<sup>®</sup> and the aim to establish a 2nd European consensus. The included diversity of experience and practice patterns of 1232 summarized patient cases in Enzymatic Debridement with Nexobrid<sup>®</sup> from a variety of European geographic locations provided a broad spectrum and high level of expertise in the panel. Panelists who participated came from ten European countries: Austria, Belgium, Germany, Italy, Norway, Poland, Romania, Spain, Switzerland and United Kingdom, and encompassed plastic surgeons, burn surgeons and burn care specialists for a multi-professional panel. Every participating center had one vote per statement (12 votes altogether), regardless of the number of participants present from the center.

### 2.2. Process and meeting

Prior to the face-to-face meeting (which was scheduled in March 2019 in Frankfurt, Germany), all panelists were provided with 75 possible, pre-formulated consensus statements on enzymatic debridement for eschar removal in burns based on peer-reviewed publications and clinical relevance, suggested topics by the invited panelists, and topics for re-evaluation from the first European consensus meeting [3] for further

discussion and adaption. Statements were either re-included if they were not consented unanimously in 2017 or if they underwent re-consideration due to new experience and evidence.

The statements included the following topics: indications, pain management and anesthesia, large surface indication, timing of application for various indications, preparation and application, post-interventional wound management, skin grafting, outcome and scar and revision management, cost-efficacy, patients perspective, logistic aspects and training strategies. Due to the process, some of the topics have been modified during the panel discussion.

The consensus workshop was divided into two major sections: The first section included the presentation of a systematic review on enzymatic debridement for eschar removal in burns in order to synchronize the level of evidence for the years 2013–2018 between the panelists. The next major section consisted of discussion of all 75 pre-formulated statements; personal experience was shared by the panel and changes in wording, merging or deletion of statements were addressed and finally consented. The panelists, with one vote per center, were asked to mark agreement or disagreement with each consensus statement at the end of the debate.

All panelists were asked to reflect the consensus statements list and results by proof-reading of the final consensus manuscript and a follow-up discussion via email. Panelists were encouraged to make comments and suggestions for changes to the manuscript. The final version of the manuscript was accepted and agreed for submission by all participants.

### 2.3. Consensus agreement

Consensus agreement was achieved with reference to the first European consensus meeting [3]. In brief, the methodology employed was an agreement algorithm based on a modification of the Willy and Stellar method [20]. For this study on Enzymatic Debridement, consensus was considered when there was at least 80 percent agreement, (i.e. at least 10 of 12 participants), to each statement. The results are summarized in Tables 1–13 with the first column showing each statements serial number (1–43), the second column representing each statement, the third column displays the tally and percentage of “yes/no” votes and the fourth column summarizes whether the statement achieved consensus based upon the above mentioned criteria.

### 2.4. Standard of care (SOC)

Throughout the whole consensus process, surgical excision with tangential knives and/or hydro surgery were regarded as surgical standard of care (SOC) and if applicable compared to Enzymatic Debridement. The panelists agreed that everything that is not exclusively defined for Enzymatic Debridement, shall follow the SOC for burn eschar removal.

## 3. Results

The following topics and consensus statements are based on the summarized experience of treating 1232 patients since

**Table 1 – Consensus statements and agreement on indications of enzymatic debridement.**

No.	Consensus statement	Yes	No	Consensus
1	Classifications with regard to timing of application for ED are “immediate/very early” ( $\leq 12$ h), early (12–72 h) or delayed ( $>72$ h).	12/12 (100%)	0/12 (0%)	Yes
2	ED might be less effective in scald injuries.	12/12 (100%)	0/12 (0%)	Yes
3	There is not enough evidence to recommend ED for chemical burns.	12/12 (100%)	0/12 (0%)	Yes
4	Outpatient treatment/ED as a day case can be performed after careful patient selection in minor burns in experienced burn centers.	9/12 (75%)	3/12 (25%)	No
5	Repeated application of ED can only be recommended in exceptional cases.	12/12 (100%)	0/12 (0%)	Yes
6	ED is best indicated for mid-to deep dermal burns with mixed patterns.	12/12 (100%)	0/12 (0%)	Yes
7	ED can be applied in full thickness burns.	12/12 (100%)	0/12 (0%)	Yes
8	Application of ED as early as possible during admission can prevent burn related compartment syndrome in circumferential extremity burns.	12/12 (100%)	0/12 (0%)	Yes
9	ED applied as early as possible during admission might prevent development of burn induced compartment syndrome in extensive trunk burns.	12/12 (100%)	0/12 (0%)	Yes
10	ED cannot replace surgical release for extended trunk burns in case of established respiratory compromise.	12/12 (100%)	0/12 (0%)	Yes
11	ED is not recommended in the extremity in case of established compartment syndrome and high voltage injury.	12/12 (100%)	0/12 (0%)	Yes

**Table 2 – Consensus statements and agreement on application of Enzymatic Debridement special regions.**

No.	Consensus statement	Yes	No	Consensus
12	ED treatment of burns on the palm or sole might be indicated in selected patients but with specific mechanical treatment	12/12 (100%)	0/12 (0%)	Yes
13	ED is highly recommended for facial burns.	12/12 (100%)	0/12 (0%)	Yes
14	Orifices of the face require special protection measures to prevent from contact with product.	12/12 (100%)	0/12 (0%)	Yes
15	Ophthalmological exam after facial burns is recommended prior to and after ED treatment.	12/12 (100%)	0/12 (0%)	Yes
16	ED is recommended for perineal and genital burns.	12/12 (100%)	0/12 (0%)	Yes

**Table 3 – Consensus statements and agreement on imaging prior/after Enzymatic Debridement.**

No.	Consensus statement	Yes	No	Consensus
17	LDI is a helpful tool for identification of regions that undergo ED.	12/12 (100%)	0/12 (0%)	Yes
18	At the moment there is no evidence to support LDI after ED.	11/12 (91.7%)	1/12 (8.3%)	Yes

**Table 4 – Consensus statements and agreement on pain management and anesthesia for Enzymatic Debridement.**

No.	Consensus statement	Yes	No	Consensus
19	Regional anesthesia is recommended for ED of the isolated (upper/lower) burnt extremity.	12/12 (100%)	0/12 (0%)	Yes
20	Local anesthesia for ED is useful in minor burns.	12/12 (100%)	0/12 (0%)	Yes

**Table 5 – Consensus statements and agreement on Enzymatic Debridement for large surface treatment.**

No.	Consensus statement	Yes	No	Consensus
21	Sequential ED procedures for larger TBSA are possible with up to 15% TBSA per session.	12/12 (100%)	0/12 (0%)	Yes
22	ED of more than 15% BSA/session requires adequate monitoring and hemodynamic support and is considered as an off-label use.	12/12 (100%)	0/12 (0%)	Yes

**Table 6 – Consensus statement and agreement on timing of Enzymatic Debridement application.**

No.	Consensus statement	Yes	No	Consensus
23	Late application ( $>72$ h from injury) is possible in selected wounds after appropriate prolonged presoaking	12/12 (100%)	0/12 (0%)	Yes



**Table 7 – Consensus statements and agreement on preparation and application of Enzymatic Debridement.**

No.	Consensus statement	Yes	No	Consensus
24	Coagulopathy has to be treated prior to ED.	12/12 (100%)	0/12 (0%)	Yes
25	Hydrogel dressings can be used as an effective moisturizer to for dry eschar to improve pre-soaking.	12/12 (100%)	0/12 (0%)	Yes
26	Pre-Soaking can be scheduled overnight to synchronize the ED application with the day shift team.	12/12 (100%)	0/12 (0%)	Yes
27	Pretreatment with silver sulfadiazine or betadine should be avoided	12/12 (100%)	0/12 (0%)	Yes
28	Persistent dry eschar after pre-soaking requires superficial surgical debridement prior to ED.	12/12 (100%)	0/12 (0%)	Yes
29	Shortening of the application time of the product <4 h cannot be recommended.	11/12 (91.7%)	1/12 (8.3%)	Yes

**Table 8 – Consensus statements and agreement on post-interventional wound management after Enzymatic Debridement.**

No.	Consensus statement	Yes	No	Consensus
30	Immediate post-ED wound bed color, bleeding patterns and 3D morphology should be assessed by an experienced burn surgeon.	12/12 (100%)	0/12 (0%)	Yes
31	A management plan with regard to further treatment modalities should be directly defined after ED by an experienced burn surgeon.	12/12 (100%)	0/12 (0%)	Yes
32	Membrane dressings and allografts can be applied after wet-to-dry phase in wounds that are expected to heal without autografting.	12/12 (100%)	0/12 (0%)	Yes
33	Allografts can be applied temporarily in wounds that are not expected to heal spontaneously after ED prior to autografting.	12/12 (100%)	0/12 (0%)	Yes
34	Indication for administration of antibiotics in the context is equivalent to surgical eschar removal.	12/12 (100%)	0/12 (0%)	Yes

**Table 9 – Consensus statements and agreement on autologous skin transplantation after Enzymatic Debridement.**

No.	Consensus statement	Yes	No	Consensus
35	In case of full thickness burns after ED, autologous skin grafting should be delayed for at least 2 days.	12/12 (100%)	0/12 (0%)	Yes
36	Deep dermal burn wounds may benefit from early autografting.	12/12 (100%)	0/12 (0%)	Yes
37	Autologous skin grafting should be considered after 21 days if there is no significant progress in epithelization.	11/12 (91.7%)	1/12 (8.3%)	Yes

**Table 10 – Consensus statements and agreement on outcome, scars and revision management after Enzymatic Debridement.**

No.	Consensus statement	Yes	No	Consensus
38	Scar treatment and prevention of hypertrophic scars is performed according to established standard protocols in burn care (Compression garments, silicon and abstention from UV-radiation).	12/12 (100%)	0/12 (0%)	Yes
39	Prolonged conservative treatment after ED may result in unstable scarring with intensive wound care, and regular reconsideration should be given for autografting.	12/12 (100%)	0/12 (0%)	Yes

**Table 11 – Consensus statement and agreement on cost-effectiveness of Enzymatic Debridement.**

No.	Consensus statement	Yes	No	Consensus
40	ED may help to reduce usage of resources (blood products, surgery, OR room capacity, human resources)	12/12 (100%)	0/12 (0%)	Yes

**Table 12 – Consensus statement and agreement on the patients perspective after Enzymatic Debridement.**

No.	Consensus statement	Yes	No	Consensus
41	Data on the patients experience on ED are rare and future research on patient experience is needed.	12/12 (100%)	0/12 (0%)	Yes

**Table 13 – Consensus statements and agreement on logistic aspects for implementation and training strategies/learning curve for Enzymatic Debridement.**

No.	Consensus statement	Yes	No	Consensus
42	ED can be performed in the operating theatre, intensive care unit or regular ward dependent on the TBSA treated and the anesthesia regimen.	12/12 (100%)	0/12 (0%)	Yes
43	ED is a specialist procedure that requires specific training, adaption to infrastructure as well as multiprofessional involvement.	12/12 (100%)	0/12 (0%)	Yes

2013 and in accordance with the recent literature. The statements were agreed upon during the 2nd European consensus meeting in March 2019 and finally included 43 statements of the 75 initially submitted to the panelists. The final list of recommendations in this paper is the result of modification, merging, and deletion of the initial statements and adaption of new topics during the panel discussion.

### 3.1. Consensus statements on indications

- 1 Classifications with regard to timing of application for ED are immediate/ very early (" $\leq 12$  h), "early" (12–72 h) or "delayed" ( $>72$  h). [12/12]

A definition of the different timings of Enzymatic Debridement is essential for this relatively new technique to provide the strategies, concepts and special measurements behind, to compare results and apply the product in view of the manufacturer's guidelines or willfully as an off-label indication:

**"Very early/ immediate"** (within 12 h after trauma) describes enzymatic debridement during the admission process, in which most of the burn wounds are still moist and do not require pre-soaking. It also includes patients after admission with initiated resuscitation phase, who due to increasing edema benefit from enzymatic debridement as an alternative strategy for surgical escharotomy to prevent burn-induced compartment syndrome.

**"Early"** (between 12 and 72 h after trauma) enzymatic debridement is regarded as the gold standard in order to take advantage of the primary benefits of enzymatic debridement. It should be applied according to the manufacturer's recommendations or according to preceding publications, e.g. the 1<sup>st</sup> European consensus guidelines [3].

**"Delayed"** (more than 72 h after trauma) enzymatic debridement is regarded as feasible, but may require additional pretreatment, e.g. mechanical removal of crusts or dry debris as well as prolonged pretreatment, e.g. pre-soaking.

Dryness is a common and classic feature of full thickness burns, because contact with hot surfaces and exposure to flames are a common mechanism of injury. If delay due to scheduled secondary referral is an issue and full thickness burns are expected, initiation of presoaking by wet dressings with antiseptic solution on burned skin before transfer may help avoid this desiccation.

Patients not responding to Enzymatic Debridement should have their compartment pressures monitored as part of the protocol with the option of converting to escharotomy in case of deterioration.

The panel agrees that both more experience and research is of benefit including more specific classification features of burns and use of its definition and their related tracks for enzymatic debridement in daily routine, as pretreatment differs and may significantly affect the outcome.

- 2 Enzymatic debridement might be less effective in scald injuries. [12/12]

Incomplete removal of scalds has been seen after Enzymatic Debridement, which may derive from the extent of depth of the zone of stasis which develops delayed as burn wound progression, especially in old patients. Due to potential deepening, Enzymatic Debridement should be applied "delayed", as incomplete removal of scalds has most frequently occurred after "early" enzymatic debridement. The pathophysiology of the scald burn per se is regarded as a potential drawback of the technique in scalds. Stepwise degradation of the dermal fibers may impede the efficiency of Enzymatic Debridement. Most scalds occur in children, where Enzymatic Debridement is still an off-label-use. In children with scald injuries, the panelists agree that the success of ED and "delayed" application is higher than in older patients.

- 3 There is not enough evidence to recommend enzymatic debridement for chemical burns. [12/12]

Chemical burns are considered to result in dry surfaces, which hinder Enzymatic Debridement to penetrate the eschar. Some chemical agents may interfere with or inactivate the active enzymes. They are difficult to be standardized according to agent and concentration. The panelists agree that individual decisions, depending on type and concentration of the agent are necessary. One center has experience with 3 cases of sulfuric acid with each receiving 2 applications. Altogether, 4 centers treating 8 patients have experience with mixed results with additional application. Currently, there is no clear evidence that supports use of Enzymatic Debridement in chemical burns.

- 4 Outpatient treatment/ED as a day case can be performed after careful patient selection in minor burns in experienced burn centers. [9/12]

Based on the methodology of this study, no consensus was achieved for the treatment of minor burns by enzymatic debridement as ambulatory care. Application of Enzymatic Debridement in minor burns to the distal extremity, with a maximum of up to approximately 2% TBSA burns may be an effective procedure with local or regional anesthesia, and



seems to be technically feasible in an outpatient setting. Ambulatory care in general may have benefits, such as reduced overall treatment costs and improved quality of life for some patients. Nevertheless, appropriate aftercare is necessary to keep the level of quality of burn treatment, which benefits from special infrastructure and is regarded as one of the major concerns resulting in “no consensus” without further evidence.

- 5 Repeated application of ED can only be recommended in exceptional cases. [12/12]

Incomplete debridement after Enzymatic Debridement may derive from technical issues during application or deepening in cases where Enzymatic Debridement has been applied too early. Repeated application in cases after deepening of the burn wound is not recommended. Repeated application is only recommended in cases where technical issues are clearly identified as the reason for failure of Enzymatic Debridement (loss of contact of enzyme, product leakage, concentration of enzyme etc.), and it is clear that these patients may still benefit from Enzymatic Debridement by a re-application.

- 6 ED is best indicated for mid-to deep dermal burns with mixed patterns. [12/12]

The surgical excision of post burn necrotic tissue has been shown to include healthy, unburned tissue up to an extent, which correlates with the surgeon's experience, concentration and type of knife. The surgeons ability to accurately excise is expected to decrease in mixed patterns, where burnt areas to be excised are in close proximity to areas which have the potential to heal. A biopsy guided- study to demonstrate the strength of Enzymatic Debridement has been published, underlining the ability to preserve healthy tissue, but altering the dermal morphology and thus requiring special post-interventional wound management [13]. The panelists' experience underlines the indication for mid-to deep dermal burns with mixed patterns, where Enzymatic Debridement exerts its strength by a selective approach.

- 7 ED can be applied in full thickness burns. [12/12]

Enzymatic Debridement exerts its strength in mid-to deep dermal burns with mixed patterns to preserve as much viable dermis as possible for improved functional outcome.

Its application in full thickness burns can be regarded as a useful indication, to reduce the time to complete eschar removal, e.g. in case of lack of operation theatre availability.

This is also the case in technically demanding areas and in areas where subcutaneous layers are very thin, it may help preserve functional structures – even if the preservation of dermis is not the primary aim.

- 8 Application of ED as early as possible during admission can prevent burn related compartment syndrome in circumferential extremity burns. [12/12]

Burn-induced compartment syndrome (BICS) is a severe sequela following circumferential burns of the extremities.

Immediate release of the increasing compartment pressure has the potential to prevent BICS by incising or removing the eschar. Surgical escharotomy is regarded as the current gold standard, but carries the risk of considerable morbidity. If specific contraindications are respected, Enzymatic Debridement is a safe and effective alternative for the prevention of BICS after deep circumferential burns at the upper extremity, thus making operative escharotomy unnecessary in many cases [6]. Fischer et al. demonstrated the feasibility and safety of Enzymatic Debridement for the prevention of operative escharotomy in circumferential deep burns of the distal upper extremity [12]. It should be applied as early as possible (“very early”), and should not be delayed by presoaking. The technique of surgical escharotomy should be kept available from the point of surgical skills and competence, and the extremity treated by Enzymatic Debridement to prevent BICS benefits from close re-evaluation – which does not differ from surgical escharotomy [6,12]. In an experimental setting, Enzymatic Debridement was shown to release increasing compartment pressure within 30 min [21].

The experience of the panelist also includes “very early” Enzymatic Debridement of the chest and neck to prevent from restriction and further complications by circular eschar on airway and breathing. The results of the panelist consistently include appropriate and effective results.

- 9 ED applied as early as possible during admission might prevent development of burn induced compartment syndrome in extensive trunk burns. [12/12]

Analogous to the effect of very early/immediate application of Enzymatic Debridement on circumferential burns to the extremities, there might be a positive effect for trunk burns to prophylactically release eschar related intra-abdominal pressure or improve thoracic wall excursion to improve resistance related breathing and ventilation restrictions. Currently, there is no evidence which has systematically evaluated this issue.

- 10 ED cannot replace surgical release for extended trunk burns in case of established respiratory compromise. [12/12]

In case of acute respiratory failure due to circumferential trunk burns, surgical escharotomy to release the pressure is mandatory.

- 11 ED is not recommended in the extremity in case of established compartment syndrome and high voltage injury. [12/12]

Due to a different pathophysiology, the incapability of the enzyme to dissolve vital fascial structures and the limited experience with Enzymatic Debridement for this indication, the panelists do not recommend the technique to release an established compartment syndrome. In a high voltage injury, the affected extremity is usually characterized by both a dermal eschar and deep tissue damage below the fat layer, such as muscle and fascia, which triggers inflammatory processes of deep edema with risk of sub-fascial compartment syndrome. These extremities benefit from surgical fasciotomy. However, ED

can be used as an adjunctive treatment after surgical decompression for dermal eschar removal.

### 3.2. Consensus statements on special regions

#### a. Hand/foot

- 12 ED treatment of burns on the palm or sole might be indicated in selected patients but receives specific mechanical treatment. [12/12]

The treatment of hands is one of the most frequently evaluated fields of interest in Enzymatic Debridement in the last 5 years. Recently, Cordts et al. summarized their experience with Enzymatic Debridement for hands and the upper extremity under regionally administered anesthesia showing that no further surgical intervention was undertaken in 53.8 % of patients, and the skin-grafted areas could be reduced by 37.0 % when compared to initial assessment in patients who underwent further skin grafting. The time from injury to ED was 24.4 h, and patients were able to start physical therapy after 2.0 days but suffered from prolonged wound closure (28.0 days) [4]. In a comparative study between SOC and Enzymatic Debridement on hands, Schulz et al. demonstrated that Enzymatic Debridement significantly reduced time to complete debridement after admission (0.95 day vs 7.750 days;  $p < 0.001$ ) and number of treatments needed for complete debridement (1.05 vs 1.45;  $p < 0.001$ ). In line with the preceding results, the number of wounds with autografting was reduced (15% vs 95%;  $p = 0.034$ ), as was time to complete healing after first debridement (23.30 vs 32.00 days;  $p < 0.001$ ). Scar quality for the hands and early scar quality after 3 months was nearly equivalent, with only increased local redness after Enzymatic Debridement [9]. Krieger et al. evaluated the concept of Enzymatic Debridement in hand burns in another comparative study and showed that the number of hands that needed surgical excision (12.9% vs 70.7%) and the mean percentage of burn wound area excised ( $4.4 \pm 13.1\%$  compared to  $52.0 \pm 41.4\%$ ) was smaller than in the SOC group. No surgical escharotomies were done compared to 9.7% in the SOC group [6].

The panelists agree, that especially in contact burns in children with a thinner epidermal layer Enzymatic Debridement works well, after mechanical pre-treatment including removal of keratin remnants.

Diabetic foot burns and patients with vascular occlusive disease may suffer from developing further eschar and deepening of their wounds and thus show disappointing results [16]. The panelists agree that this cohort rarely benefits from Enzymatic Debridement.

Hands, feet and extremities may serve as a well-chosen region for the introduction of Enzymatic Debridement in a burn center, but potential pit-falls and a special in-house debridement treatment algorithm should be obeyed [8].

#### b. Face

- 13 ED is highly recommended for facial burns. [12/12]

Due to its unique anatomy in line with high demands on preservation of dermis due to the functional and aesthetic

benefits, Enzymatic Debridement shows its strengths of selective eschar removal in the face.

Schulz et al. evaluated the application of Enzymatic Debridement for deep facial burns and compared it to SOC. They showed that Enzymatic Debridement significantly reduced time to complete wound closure after admission (19.85 days versus 42.23 days,  $p = 0.002$ ). The number of procedures to complete debridement was significantly lower in the enzymatic debridement group (1.00 versus 1.77,  $p = 0.003$ ). Wounds undergoing autografting of any size were significantly reduced by Enzymatic Debridement (15% versus 77%,  $p = 0.002$ ). Scar quality after Enzymatic Debridement was superior compared to surgical debridement after 12 months regarding pigmentation ( $p = 0.016$ ), thickness ( $p = 0.16$ ), relief ( $p = 0.10$ ), pliability ( $p = 0.01$ ), surface area ( $p = 0.004$ ), stiffness ( $p = 0.023$ ), thickness (0.011) and scar irregularity ( $p = 0.011$ ). In regard to erythema and melanin, viscoelasticity and pliability, trans-epidermal water loss or laser tissue oxygen saturation, hemoglobin level and microcirculation no significant differences for treated and untreated skin in the Enzymatic Debridement group were found [10].

We find it important to point out that the safe application of Enzymatic Debridement in the face requires special preparations of the sensory organs to protect them from contact with the enzyme. The panelists agree that application in the face requires significant experience with Enzymatic Debridement and this region should not be chosen by those only beginning their Enzymatic Debridement treatment experience.

- 14 Orifices of the face require special protection measures to prevent them from contact with product. [12/12]  
15 Ophthalmological exam after facial burns is recommended prior to and after ED treatment. [12/12]

#### c. other regions

- 16 ED is recommended for perineal and genital burns. [12/12]

In general, the literature on perineal and genital burns is scarce and favors long-lasting conservative treatment pathways prior to surgery to promote spontaneous healing because reconstruction does not always lead to satisfying results. Enzymatic Debridement may allow earlier and more selective debridement, which can improve the outcome [11].

As perineal and genital burns benefit from advanced surgical skills in terms of treating concave and convex regions in close proximity Enzymatic Debridement may reveal its ability to preserve viable dermis and prevent injury to vital structures by the surgeon's knife.

### 3.3. Consensus statements on imaging

Accurate evaluation of the burn wound is an essential part of goal-directed, individual burn treatment, which is a keystone supporting the concept of Enzymatic Debridement. Imaging modalities in burn treatment have been evaluated to quantify the evaluation of the depth and extent of the burn. Laser Doppler Imaging (LDI) is regarded as the superior imaging modality compared to other techniques, e.g. thermal imaging

or clinical assessment, in terms of diagnostic accuracy [22,23]. LDI allows differentiation between burns that will heal without skin grafting and burns that undergo skin grafts after Enzymatic Debridement.

- 17 LDI is a helpful tool for identification of regions that undergo ED. [12/12]

LDI is recommended in addition to clinical evaluation of burn depth and aims to predict healing of the burn wound within 21 days. It should be used after 48 h as blue scans on early LDI are not helpful. [24–26]. Seven out of 12 centers use LDI systems, and 5 out of 7 have experience in LDI use in the context of Enzymatic Debridement. LDI is regarded as useful to predict regions which benefit from early grafting after Enzymatic Debridement. The panelists agree that LDI is the imaging tool of choice to be integrated into the selective, individualized concept of Enzymatic Debridement.

- 18 At the moment there is no evidence to support LDI after ED. [11/12]

Currently there is no evidence that LDI is a helpful tool for wound bed assessment **after** Enzymatic Debridement. Three panelists have basic experience in the use of LDI after Enzymatic Debridement, without a clear recommendation for its application. Based on their experience, LDI is not reliable after Enzymatic Debridement, as there is no correlation between scan image and a clinical consequence.

### 3.4. Consensus statements on pain management and anesthesia

Enzymatic Debridement is a selective, dermis-preserving concept for eschar removal. Underestimation of its invasiveness may lead to inappropriate anesthesia and even for the need for rescue analgesia [27]. Enzymatic Debridement is a painful procedure and requires sufficient analgesia and/or anesthesia [4,27]:

- 19 Regional anesthesia is recommended for ED of the isolated (upper/lower) burnt extremity. [12/12]  
20 Local anesthesia for ED is useful in minor burns. [12/12]

Four out of 12 panelists report experience with local anesthesia, and all panelists have experience with regional anesthesia. During the first consensus process in 2017, only 7 out of 12 panelist agreed to the use of regional anesthesia [3]. For regional anesthesia use of catheter therapy or a single shot with long-lasting locally acting anesthetic drugs is preferred in view of safety issues and pain profile of Enzymatic Debridement. Analgesedation is preferable over general anesthesia.

Depending on the treated TBSA and patient conditions, Enzymatic Debridement requires minimum monitoring standards during treatment independent of anesthesia technique (i.v. line, pulse oximetry, access to monitoring, physician on call)

### 3.5. Consensus statements on ED for large surface treatment

- 21 Sequential ED procedures for larger TBSA are possible with up to 15% TBSA per session. [12/12]  
22 ED of more than 15% TBSA/session requires adequate monitoring and hemodynamic support and is considered as an off-label use. [12/12]

Enzymatic Debridement for eschar removal is formally limited to 15% treated TBSA per application by regulation issues and approval. Principal advantages of the technique have raised the idea of treating >15% TBSA per application session. 5 out of 12 panelists have experience with more than 15% TBSA treatment per session. The panelists agree that Enzymatic Debridement of large surfaces may produce increased surface water loss and requires adapted resuscitation/ volume management.

Scheduling a sequential ED procedure requires a stable patient without an increased bleeding tendency. There are concerns among the panelists in respect to a maximum of one application session/day, analogous with a single surgical procedure per day in SOC.

Currently there is no appropriate evidence to support the use of Enzymatic Debridement for larger TBSA of > 15%. In addition, there is a lack of evidence on the systemic response/reduction of systemic response and on early large surface use as a sub-entity.

### 3.6. Consensus statement on timing of application

Due to pre-soaking as a preparative dressing to ED, timing is very flexible except for “immediate” ED to prevent BICS (see also statement 1). Generally, there is no regulatory or clinical contraindication for late application, e.g. in case of late transfer to the burn center. Wounds should be carefully selected to provide all requirements for Enzymatic Debridement, including rehydration of the eschar by prolonged presoaking and total removal of any external ointments, which might interfere with the enzyme. Late application >72 h from injury has not been addressed in the literature frequently, as the majority of clinical trial experience is from patients treated within 72 h from injury [1].

- 23 Late Application (>72 h from injury) is possible in selected wounds after appropriate prolonged presoaking. [12/12]

### 3.7. Consensus statements on preparation and application

Protection of the burn team is mandatory for the application of Enzymatic Debridement for eschar removal, and has to include protection measures analogous to a surgical procedure (e.g. protective glasses).

The panelists are aware of 2 cases of severe allergic reaction potentially related to the application of the product. This rare event has to be considered prior to and during treatment, and immediate abortion of the therapy by removal of the product should be considered accompanied by appropriate therapy.

#### 24 Coagulopathy has to be treated prior to ED. [12/12]

Enzymatic Debridement is a powerful tool and has been developed and validated to be more selective compared to the SOC. In view of this power, it must be clearly emphasized, that peri-procedural bleeding will occur and activity of the coagulation system is essential — as it is for surgical burn wound excision. As severely burnt patients may suffer from coagulopathies in about 40% [28], these have to be treated prior to Enzymatic Debridement. This is even more important when large surfaces are treated in one session. There is one case report in the literature, that describes a potential interaction between Bromelain and hemostasis, as after intervention close to the time of application a coagulation disorder occurred [28]. The panelists have not experienced any comparable case yet, but attention should be raised to peri-procedurally checking the coagulation and quickly responding in case of any coagulopathy.

#### 25 Hydrogel dressings can be used as an effective moisturizer for dry eschar to improve pre-soaking. [12/12]

Hydrogel based dressings with an antiseptic active agent are regarded as effective dressing to improve the moisturizing process during pre-soaking. Due to approval regulations and sourcing strategies, local, regional, and international variations in the availability of rinsing solutions and hydrogels with antiseptic activity exist and may indirectly influence the results of treatment. In a recent study, Schulz et al. addressed various agents and their capability to inhibit enzymatic debridement activity in vitro. Based on this study, polyhexanide-containing agents are recommended to rinse and pre-soak burn wounds prior to Enzymatic Debridement [29]. Experimentally, the authors found a partial inhibition of enzymatic activity at the distinct pH values of 3 and 11 [29].

#### 26 Pre-Soaking can be scheduled overnight to synchronize the ED application with the day shift team. [12/12]

The statements include a deviation from published and standardized protocols, as pre-soaking is recommended for a least 2 h. Nevertheless, the panelists agree that logistical disadvantages may prevent implementation, and regard prolonged soaking as a helpful strategy. In addition, the panelists agree that prolonged post-soaking could be beneficial to reduce the amounts of Enzymatic Debridement remnants with potential impact on pseudoeschar.

#### 27 Pretreatment with silver sulfadiazine or betadine should be avoided. [12/12]

There is recent evidence from in vitro studies, that pretreatment of burn wounds with agents containing silver and copper should be avoided due to interference with enzymatic activity [29].

#### 28 Persistent dry eschar after pre-soaking benefits from superficial surgical debridement prior to ED. [12/12]

Pre-treatment is necessary as ED does not penetrate keratin/ epidermis and dry eschar down to moist eschar. Superficial, mechanical pretreatment with curettes etc. is recommended if Enzymatic Debridement is chosen for selected eschar removal, but crusty, dry or epidermolytic eschar tissue prevents sufficient penetration of the enzyme.

#### 29 Shortening of the application time of the product <4 h cannot be recommended. [11/12]

All panelists have experience and success in applying the product for 4 h (or more because of logistical reasons), which is the primary method in all published studies.

There is recent experimental evidence, that macrophage activity during the inflammatory response after application of Enzymatic Debridement results in protection of viable cells and leads to inactivation of the enzyme after 4 h [30]. There was not unanimous consensus on the statement, as one panelist has experience with shorter application. Experience is only limited to intermediate dermal burns, where durations of 2 h seem to be sufficient. No experience on shorter application phases for deep dermal or full thickness burns exist.

### 3.8. Consensus statements on post-interventional wound management

The panelists agree, that post-Enzymatic Debridement wound bed appearance and bleeding patterns are essential in the evaluation and deciding the ideal treatment pathway after Enzymatic Debridement. In general, after Enzymatic Debridement, a decision should be made whether to follow an early coverage pathway with grafting techniques or a conservative pathway with prolonged observation time compared to regular burn wounds.

Assessment of the wound bed color, bleeding patterns and 3D morphology is one of the most essential but also demanding tasks during the implementation process for Enzymatic Debridement.

#### 30 Immediate post-ED wound bed color, bleeding patterns and 3D morphology should be assessed by an experienced burn surgeon. [12/12]

The evaluation of the post-Enzymatic Debridement wound bed is one of the most decisive steps in successful and sustainable application of Enzymatic Debridement, and has to consider the wound bed color and the bleeding pattern of the whole treated area. Schematic drawings and photography of both wound bed color and the bleeding pattern are essential, to document the treatment results, especially in a large team. This issue has been addressed in detail in the first European Consensus Publication on Enzymatic Debridement [3].

#### 31 A management plan with regard to further treatment modalities should be directly defined after ED by an experienced burn surgeon. [12/12]

Based on the wound bed color and the bleeding pattern of the whole treated area, an individual management plan



should be addressed, either to put the area(s) on a 1. *Early grafting* or 2. *Secondary healing pathway*. In order to reduce further bleeding and donor sites for skin grafting, each treated area benefits from an individual management plan. Further issues include minimally invasive techniques for secondary debridement immediately prior to skin grafting or (e.g. Hydrosurgery), and concepts to keep the secondary wound healing process in areas without skin grafting optimal (e.g. moisture). Further pseudoeschar, which is characteristic for Enzymatic Debridement, is believed to be part of the healing process and *not a sign of therapeutic failure*. When pseudoeschar has been finally established, re-evaluation of the wound bed in view of grafting vs. secondary healing is *technically impossible*. This issue has been also addressed in further detail in the first European Consensus Publication on Enzymatic Debridement [3].

- 32 Membrane dressings and allografts can be applied after wet-to-dry phase in wounds that are expected to heal without autografting. [12/12]

There is evidence from the literature that membrane dressings (e.g. Biobrane<sup>®</sup>, Suprathel<sup>®</sup>) are useful after Enzymatic Debridement in wounds that are not assessed and scheduled for grafting [31]. The panelists agree that a decisive and individualized post-interventional wound management is an essential part of the concept and the key to success of Enzymatic Debridement. Post interventional management is strictly influenced by the individual availability of antiseptic solutions and specific wound dressings, but some basic issues should be considered in general. In a recent study Di Lonardo et al. analyzed the effect of Enzymatic Debridement on mid-deep partial thickness wounds, and observed that partially damaged dermis was always spared by the enzymatic activity. This dermis showed some "homogenization" characteristics, had few vital skin adnexal structures in it, and therefore looked very similar to the scaffold of dermal matrices currently available on the market [13].

- 33 Allografts can be applied temporarily in wounds that are not expected to heal spontaneously after ED prior to autografting. [12/12]

Allograft represents a nearly ubiquitous available wound dressing, which involves all relevant characteristics for an appropriate wound dressing after Enzymatic Debridement if not expected to heal spontaneously. Nevertheless, regulatory limitations, general availability and costs may be an issue.

- 34 Indication for administration of antibiotics is equivalent to surgical eschar removal. [12/12]

Burn wounds provide an ideal platform for bacterial proliferation and a point of entry into the bloodstream, mostly due to epithelial barrier loss and temporary immunosuppression which predispose burn patients to infections. Indication for administration of antibiotics during Enzymatic Debridement for eschar removal should be regarded as equivalent to SOC.

A meta-analysis of several studies on systemic, **perioperative prophylaxis** (2 weeks) revealed a positive effect of

prophylactic antibiotic therapy, but limited validity due to the low methodological quality of included studies and limited comparability [32]. Early colonization by *Pseudomonas aeruginosa* was even more common in the prophylaxis group than the non-prophylaxis group. A recent Cochrane review concluded that the benefits of prophylaxis in preventing burn wound infections was still unclear [33]. In a systematic review, antimicrobial prophylaxis was shown to be useful in patients with severe burns receiving mechanical ventilation (Grade 2B) [34]. As a result, prophylaxis cannot be recommended based on the recent literature without restrictions, in relation to side effects and costs of antibiotic therapy [32,35].

**In contrast, peri-interventional and perioperative therapy** is chosen in surgery of the burn wound to reduce bacterial load and bacteremia and associated increased graft infection rates. It is recommended to administer a single shot, which can be extended up to 48 h postoperatively. It can be prolonged, if surgical debridement, resection and decontamination is limited. Nevertheless, the evidence still is limited [36]. In patients with minor burns and perioperative therapy with a cephalosporin, a lower incidence of donor site infection was shown, but without effects on the burn site [37]. In a systematic review, perioperative therapy during resection of devitalized tissue is of no benefit in most burn patients (Grade 2B); however, there was not sufficient evidence to make a recommendation for patients with extensive burns. Antibiotic prophylaxis may also be effective in preventing split-thickness skin graft infections in selected procedures (Grade 2B) [34].

### 3.9. Consensus statements on autologous skin grafting

The panelists agree that grafting after Enzymatic Debridement remains one of the most challenging issues on decision-making in order to balance between the selective concept of Enzymatic Debridement to reduce the rate of blood loss and removal of healthy tissue and the clinical needs to prevent patients from delayed, inappropriate burn wound healing and associated reduced functional outcome. In future, it still requires an open discussion and individual experience. Even based on the huge, summarized experience of the panelists, no conclusive statements are possible, as the decision to indicate autologous skin transplantation is dependent on several patient individual factors. These factors include the post-interventional-bleeding pattern of different treated areas, 3D wound bed morphology, time to heal and regions of interest. Until now, no evidence supports a distinct time point for transplantation dependent on the depth and bleeding pattern, which has been shown to be superior. The panelists intended to guide the applicants in the decision-making process on autologous skin transplantation as follows:

- 35 In case of full thickness burns after ED, autologous skin grafting should be delayed for at least 2 days. [12/12]

In order to gain back cellular wound bed integrity and to limit secretion and local bleeding after the procedure, autologous skin grafting should be postponed for at least two days to improve graft take rates. The decision is based on the post-interventional bleeding pattern.

- 36 Deep dermal burn wounds may benefit from early auto-grafting. [12/12]

Early closure should be addressed, when fat layers and thrombosed veins are visible after Enzymatic Debridement. In these deep dermal wounds, additional eschar removal may be addressed by minimal-invasive surgical techniques, e.g. Hydrosurgery. The post-interventional bleeding pattern may guide the surgical decision.

- 37 Autologous skin grafting should be considered after 21 days if there is no significant progress in epithelization. [11/12]

In superficial to mid-dermal/deep-dermal wounds with an appropriate LDI and bleeding-pattern suggesting secondary healing, skin transplantation is not primarily scheduled, as healing without transplantation is regarded to have a superior outcome in these patients and pseudoeschar as a typical product of the treatment may not allow later interpretation [1,10]. Nevertheless, if secondary healing is significantly delayed, procrastination in regard to autologous skin transplantation may result in unstable scarring and functional limitations.

In order to address this most debatable issue, in the 1<sup>st</sup> consensus meeting on Enzymatic Debridement in burns, with a consensus of 7 out of 10 panelists, it was stated that "Autologous skin grafting is advisable at latest after 21 days if there is no progress in epithelization." [3]. In the 2<sup>nd</sup> consensus meeting, which is based on a significantly higher experience of cases treated with Enzymatic Debridement, this very statement was rephrased – resulting in a consensus of 11 out of 12 (91.6%).

Keratinocyte-Suspension may support re-epithelization and is less invasive compared to skin grafts. Two centers have experience with Keratinocyte-Suspensions as an adjunct to improve secondary healing, but the panelists agree that further evaluation is required before a general recommendation is justified.

### 3.10. Consensus statements on outcome, scars and revision management

- 38 Scar treatment and prevention of hypertrophic scars is performed according to established standard protocols in burn care (Compression garments, silicon and abstention from UV-radiation). [12/12]

After Enzymatic Debridement there is a risk profiling for delayed wound healing in burn wounds: all wounds that take > than 3 weeks for healing or skin grafted wounds after Enzymatic Debridement benefit from full anti-scar therapy for at least one year. This consists of pressure garments, silicone garments or sheets, inlays, moisturizers, physical therapy, sometimes additional surgery). Further evidence on the mid- to long-term outcome on these issues is not available yet.

- 39 Prolonged conservative treatment after ED may result in unstable scarring with intensive wound care, and regular reconsideration should be given for autografting. [12/12]

Prolonged conservative treatment after day 21 is a very demanding option, as the risk for unfavorable scarring after delayed healing maybe higher compared to autologous skin grafting.

### 3.11. Consensus statements on cost-effectiveness

- 40 ED may help to reduce usage of resources (blood products, surgery, OR room capacity, human resources). [12/12]

Enzymatic Debridement is a useful tool, which may help to reduce classical resources for surgical burn eschar removal. While surgical eschar removal is traditionally applied in the operation room, Enzymatic Debridement is done at the burn ICU or a regular burn ward. The surgeon is not required during the whole therapy of Enzymatic Debridement. Only secondary skin transplantation has to be scheduled in the operation room, but with reduced surface area [14,15]. In addition, the selective approach of Enzymatic Debridement may help to reduce blood product resource as demonstrated before [1]. In view of various health care systems of the participating panelist and in general, there must be chosen an individual approach to analyze and communicate cost-effectiveness, which is dependent on individual reimbursement of Enzymatic Debridement, channeled by the national health care system.

### 3.12. Consensus statements on the patient's perspective after ED

- 41 Data on the patients experience on ED are rare and future research on patient experience is needed. [12/12]

Patient reported outcome measures (PROMSs) are under reported in the current literature. Patients report significant pain during and after ED. Therefore adequate analgesia is essential. Pain is the only outcome parameter and only addressed in one paper [4]. Patients reported scar assessment is addressed in most of the recent articles.

### 3.13. Consensus Statements on Logistic aspects for implementation and Training strategies/learning curve

- 42 ED can be performed in the operating theatre, intensive care unit or regular ward dependent on the TBSA treated and the anesthesia regimen. [12/12]

- 43 ED is a specialist procedure that requires specific training, adaption to infrastructure as well as multi-professional involvement. [12/12]

Implementation of ED requires individual SOPs, adapted to house lists (dressings, external ointments, active dressing's gauze) and logistics. A steep learning curve may necessitate further training. It is imperative to create enthusiasm for this method of debridement which often requires more effort from the surgeons, the nurses and the anesthesiologists/intensive care doctors who are in charge of pain management and resuscitation of the patient



A relevant learning curve is obvious, but logistics issues may require even more attention.

### 3.14. Areas of future research and future issues

The panelists agreed that there are several relevant issues, which should be addressed in future, both in clinical and experimental research on Enzymatic Debridement. These issues in particular include the patients perspective, systemic inflammatory response and systemic effect of Bromelain after Enzymatic Debridement. In addition, the panelists recommend establishing a registry/database of all patients treated with Enzymatic Debridement for further evaluation of this promising technique. A biennale Consensus Workshop is recommended to be held due to its ongoing development.

## 4. Discussion

After its approval in Europe in 2013, Enzymatic Debridement with Nexobrid® as an additional tool for a more individualized, selected and less invasive burn eschar removal has gained significantly increasing attention and application rates among burn surgeons worldwide during the last 5 years [6,31]. The summarized experience of 1232 treated patients reflects the significance of the provided user-orientated recommendations for a successful implementation and application of Enzymatic Debridement for eschar removal. Compared to the first summarized experience of the panelist with approximately 500 patients additional 700 patients have been treated as the basis of this consensus document. [3].

Forty-three statements were formulated, addressing the topics: indications, pain management and anesthesia, large surface indication, timing of application for various indications, preparation and application, post-interventional wound management, skin grafting, outcome, scar and revision management, cost-effectiveness, patients perspective, logistic aspects and training strategies. The degree of consensus was high, with consensus in 42 out of 43 statements (97.7%), while no consensus was achieved on the role of outpatient treatment/ED as day cases in minor burns in experienced burn centers. A classification with regard to timing of application for Enzymatic Debridement was introduced, with immediate/very early ( $\leq 12$  h), early (12–72 h) or delayed ( $>72$  h) treatment.

The potential of outpatient treatment remains a relatively new controversial issue, as it principally raises further benefits of the concept. In contrast, LDI and skin grafting remain controversy topics, but with further clarifications and recommendations, and a higher degree of consensus, than in the first European Consensus Meeting in 2017 [3].

Enzymatic Debridement may show its advantages in severely burned patients, as it allows very early, less-traumatic removal of necrotic tissue even in patients whose overall clinical conditions would mandate delaying traditional surgical eschar removal.

The increasing experience in the application of Enzymatic Debridement also reveals some limitations, which are useful to discuss to improve the success rates:

Berner et al. published their experience of treating burns in patients with established diabetic foot disease in a case

series. The authors described that all of these patients developed further eschar and deepening of their wounds a few days after Enzymatic Debridement, and underwent further surgery and skin grafting. Based on their limited experience they recommend avoiding Enzymatic Debridement in patients with diabetic foot wounds, as the special issues of microangiopathy seem to counteract this technique and the bleeding patterns [16].

Until now, there is no evidence that supports Enzymatic Debridement in chemical burns with potential interaction and inactivation. In addition, high voltage injuries with potential deep muscle damage and increased compartment pressures should not be treated with Enzymatic Debridement for immediate eschar removal and compartment release, as the enzyme limits its activity to the eschar and cannot release muscular compartments. Additionally, scald burns do not show comparable results after Enzymatic Debridement compared to flame burns, which is the reason not to recommend the technique in the early phase for scald burns and limited recommendation in general. The panelists agree that Enzymatic Debridement of large surfaces may be feasible, but may produce increased surface water loss and adapted resuscitation/ volume management. Furthermore, the “ideal patient” for large surface indications has to be defined, and the systemic effect of Bromelain and early eschar removal in the context of Enzymatic Debridement should be evaluated.

Several areas for treatment have been demonstrated to work well, e.g. hands [4–9] as well as burns to the face [10] and genitals [11], with most published studies and patients on hand burns. Fischer et al. demonstrated the feasibility and safety of Enzymatic Debridement for the prevention of operative escharotomy in circumferential deep burns of the distal upper extremity [12]. These findings are in line with and strengthened by the panelists’ experience. It should be applied as early as possible (“very early”), and should not be delayed by presoaking. LDI has been evaluated and identified as an important imaging device, which is linked to the concept of selective Enzymatic Debridement and is useful to predict regions which benefit from early grafting after Enzymatic Debridement [24–26].

The panel conducted an intensive debate on the use of Enzymatic Debridement in case of limited operation room capacity in the setting of a mass casualty. No statement was regarded as possible for consensus. The panelists agree that early Enzymatic Debridement in mass casualties may cause further issues, as patients may undergo further transplantation and resources such as blood products, though Rosenberg et al. have shown reduced need for blood products after Enzymatic Debridement in general [1].

### 4.1. Limitations

Although the present consensus paper refers to the summarized experience of 1232 patient cases of the panelist and is in line with the present evidence on Enzymatic Debridement including randomized-controlled trials (LoE 1) to case reports (LoE4), the present consensus reflects expert opinions (LoE5). Not all recommendations can be supported by the available literature, as this is often limited in view of practical clinical issues. In addition, not all relevant issues on Enzymatic

Debridement could be addressed or re-evaluated from the first panel meeting, as the available panel time was limited.

#### 4.2. Conclusion

The updated guidelines in this publication represent further refinements on the indication, application and post-interventional management for the use of Enzymatic Debridement. The published statements contain detailed, user-orientated recommendations aiming to align current and future users and prevent unnecessary pitfalls for the successful implementation of this promising technique. The present consensus publication aims to manage the balancing act between evidence and user-orientated recommendations base on the methodology of the panel meeting. We believe that future, regular readjustments and fine-tuning of these recommendations should be performed to define relevant study topics, and to adopt further knowledge and evidence.

#### Conflict of interest statement

In behalf of all contributing authors I declare the following potential conflicts of interest related with the present manuscript:

Dr. Hirche has been a consultant and speaker for MediWound, Germany and is on the scientific advisory board of Kinetic Concepts, Inc., Europe.

Dr. Almeland has no conflicts of interest to declare.

Mr. Dheansa has been a speaker for MediWound, UK, and a member of the data monitoring board for a study sponsored by MediWound.

Dr. Fuchs has no private disclosures. His institution received scientific grants from MediWound, Germany.

Dr. Governa has been a speaker for MediWound, Germany.

Mr. Hoeksema has been a speaker for MediWound, Germany.

Dr. Korzeniowski has been a consultant and speaker for MediWound, Germany.

Dr. Lumenta has no conflicts of interest to declare.

Dr. Marinescu has been a consultant and speaker for MediWound, Romania.

Dr. Martinez-Mendez has been a speaker for MediWound, Spain.

Dr. Plock has been a consultant and speaker for MediWound, Germany.

Dr. Sander has been a speaker for MediWound, Germany.

Dr. Ziegler has been a speaker for MediWound, Germany.

Dr. Kneser has been a consultant for MediWound, Germany.

#### Acknowledgments

The consensus workshop was initiated and hosted by BG Trauma Center Ludwigshafen, University of Heidelberg and supported by an unrestricted educational grant provided by MediWound Germany GmbH, Rüsselsheim, Germany. The grant provided financial support for a face-to-face expert panel to discuss the available peer-reviewed literature as well as

clinical experience of the experts with ED. The authors are solely responsible for the contents of this article.

#### REFERENCES

- [1] Rosenberg L, Krieger Y, Bogdanov-Berezovski A, Silberstein E, Shoham Y, Singer AJ. A novel rapid and selective enzymatic debridement agent for burn wound management: a multicenter RCT. *Burns* 2014;40:466–74.
- [2] Ozcan C, Ergun O, Celik A, Corduk N, Ozok G. Enzymatic debridement of burn wound with collagenase in children with partial-thickness burns. *Burns* 2002;28:791–4.
- [3] Hirche C, Citterio A, Hoeksema H, Koller J, Lehner M, Martinez JR, et al. Eschar removal by bromelain based enzymatic debridement (Nexobrid®) in burns: an European consensus. *Burns* 2017;43:1640–53.
- [4] Cordts T, Horter J, Vogelpohl J, Kremer T, Kneser U, Hernekamp JF. Enzymatic debridement for the treatment of severely burned upper extremities — early single center experiences. *BMC Dermatol* 2016;16:8.
- [5] Di Castri A, Quarta L, Mataro I, Riccardi F, Pezone G, Giordano L, et al. The entity of thermal-crush-avulsion hand injury (hot-press roller burns) treated with fast acting debriding enzymes (nexobrid): literature review and report of first case. *Ann Burns Fire Disasters* 2018;31:31.
- [6] Krieger Y, Rubin G, Schulz A, Rosenberg N, Levi A, Singer AJ, et al. Bromelain-based enzymatic debridement and minimal invasive modality (mim) care of deeply burned hands. *Ann Burns Fire Disasters* 2017;30:198–204.
- [7] Rigueros Springford L, Creasy H, Cubison T, Dheansa B. A novel technique of Nexobrid™ application to burns on the hands. *Burns* 2017;43:1132–3.
- [8] Schulz A, Perbix W, Shoham Y, Daali S, Charalampaki C, Fuchs PC, et al. Our initial learning curve in the enzymatic debridement of severely burned hands—management and pit falls of initial treatments and our development of a post debridement wound treatment algorithm. *Burns* 2017;43:326–36.
- [9] Schulz A, Shoham Y, Rosenberg L, Rothermundt I, Perbix W, Christian Fuchs P, et al. Enzymatic versus traditional surgical debridement of severely burned hands: a comparison of selectivity, efficacy, healing time, and three-month scar quality. *J Burn Care Res* 2017;38:e745–55.
- [10] Schulz A, Fuchs PC, Rothermundt I, Hoffmann A, Rosenberg L, Shoham Y, et al. Enzymatic debridement of deeply burned faces: healing and early scarring based on tissue preservation compared to traditional surgical debridement. *Burns* 2017;43:1233–43.
- [11] Schulz A, Ribitsch B, Fuchs PC, Lipensky A, Schiefer JL. Treatment of genital burn injuries. *Adv Skin Wound Care* 2018;31:314–21.
- [12] Fischer S, Haug V, Diehm Y, Rhodius P, Cordts T, Schmidt VJ, et al. Feasibility and safety of enzymatic debridement for the prevention of operative escharotomy in circumferential deep burns of the distal upper extremity. *Surgery (United States)* 2019;19–24.
- [13] Di Lonardo A, Nardini V, De Rosa M, Pascone C, Graziano A, Criscuoli AM, et al. Enzymatic escharolysis with Nexobrid® on partial thickness burn wounds: pre-and post-debridement histological assessment. *Ann Burns Fire Disasters* 2018;31:23–7.
- [14] Giudice G, Filoni A, Maggio G, Bonamonte D, Vestita M. Cost analysis of a novel enzymatic debriding agent for management of burn wounds. *Biomed Res Int* 2017;2017:9567498.
- [15] Kern MA, Depka NV, Schackert C, Henkel W, Hirche CR. Enzymatic burn wound debridement with Nexobrid®: cost simulations and investigations on cost efficiency.

- Gesundheitsökonomie und Qualitätsmanagement 2018;23:21–8.
- [16] Berner JE, Keckes D, Pywell M, Dheansa B. Limitations to the use of bromelain-based enzymatic debridement (NexoBrid®) for treating diabetic foot burns: a case series of disappointing results. *Scars Burn Heal* 2018;4:2059513118816534.
  - [17] Osinga R, Steiger P, Giovanoli P, Plock JA, Mannil L. Burn wound treatment through enzymatic debridement: first experience in Switzerland. *Handchir Mikrochir Plast Chir* 2018.
  - [18] Krauss S, Bender D, Rothenberger J, Daigeler A, Held M. Delayed and fractional use of enzymatic debridement with nexobrid for extensive burn injury: a case report. *Ann Burns Fire Disasters* 2018;31:28–30.
  - [19] Martin N, Guilabert P, Abarca L, Usua GM, Serracanta J, Colomina MJ. Coagulation abnormalities following NexoBrid use: a case report. *J Burn Care Res* 2018;39:1067–70.
  - [20] Willy C, SD. Literature analysis (2005–2012) on the topic antiseptics for the treatment of acute soft tissue and bone wounds following the guidelines of evidence based medicine. In: Willy C, editor. *Antiseptics in surgery*. Germany: Lindqvist Book Publishing; 2013. p. 33–81.
  - [21] Krieger Y, Rosenberg L, Lapid O, Glesinger R, Bogdanov-Berezovsky A, Silberstein E, et al. Escharotomy using an enzymatic debridement agent for treating experimental burn-induced compartment syndrome in an animal model. *J Trauma* 2005;58:1259–64.
  - [22] Wearn C, Lee KC, Hardwicke J, Allouni A, Bamford A, Nightingale P, et al. Prospective comparative evaluation study of Laser Doppler Imaging and thermal imaging in the assessment of burn depth. *Burns* 2018;44:124–33.
  - [23] Jan SN, Khan FA, Bashir MM, Nasir M, Ansari HH, Shami HB, et al. Comparison of Laser Doppler Imaging (LDI) and clinical assessment in differentiating between superficial and deep partial thickness burn wounds. *Burns* 2018;44:405–13.
  - [24] Hoeksema H, Baker RD, Holland AJ, Perry T, Jeffery SL, Verbelen J, et al. A new, fast LDI for assessment of burns: a multi-centre clinical evaluation. *Burns* 2014;40:1274–82.
  - [25] Monstrey SM, Hoeksema H, Baker RD, Jeng J, Spence RS, Wilson D, et al. Burn wound healing time assessed by laser Doppler imaging. Part 2: validation of a dedicated colour code for image interpretation. *Burns* 2011;37:249–56.
  - [26] Pape SA, Baker RD, Wilson D, Hoeksema H, Jeng JC, Spence RJ, et al. Burn wound healing time assessed by laser Doppler imaging (LDI). Part 1: derivation of a dedicated colour code for image interpretation. *Burns* 2012;38:187–94.
  - [27] Galeiras R, Mourelo M, Pertega S, Lopez ME, Esmoris I. Procedural sedation and analgesia during enzymatic debridement of burn patients. *Ann Burns Fire Disasters* 2018;31:223–7.
  - [28] Martin N, Guilabert P, Abarca L, Usua GM, Serracanta J, Colomina MJ. Coagulation abnormalities following NexoBrid use: a case report. *J Burn Care Res* 2018;39:1067–70.
  - [29] Schulz A, Fuchs PC, Hans N, Opländer C, Valdez LB, Schiefer JL. Inhibition of bromelain activity during enzymatic debridement of burn wounds pretreated with frequently used products. *J Burn Care Res* 2018;39:413–22.
  - [30] Schulz A, Fuchs PC, Oplaender C, Valdez LB, Schiefer JL. Effect of bromelain-based enzymatic debridement on skin cells. *J Burn Care Res* 2018;39:527–35.
  - [31] Rigueros Springford L, Creasy H, Cubison T, Dheansa B. A novel technique of NexoBrid application to burns on the hands. *Burns* 2017;43:1132–3.
  - [32] Avni T, Levkovich A, Ad-El DD, Leibovici L, Paul M. Prophylactic antibiotics for burns patients: systematic review and meta-analysis. *BMJ* 2010;340:c241.
  - [33] Barajas-Nava LA, Lopez-Alcalde J, Roque i Figuls M, Sola I, Bonfill Cosp X. Antibiotic prophylaxis for preventing burn wound infection. *Cochrane Database Syst Rev* 2013;CD008738.
  - [34] Ramos G, Cornistein W, Cerino GT, Nacif G. Systemic antimicrobial prophylaxis in burn patients: systematic review. *J Hosp Infect* 2017;97:105–14.
  - [35] Houschyar KS, Tapking C, Duschler D, Wallner C, Sogorski A, Rein S, et al. [Antibiotic treatment of infections in burn patients — a systematic review]. *Handchir Mikrochir Plast Chir* 2019;51:111–8.
  - [36] Durtschi MB, Orgain C, Counts GW, Heimbach DM. A prospective study of prophylactic penicillin in acutely burned hospitalized patients. *J Trauma* 1982;22:11–4.
  - [37] Griswold JA, Grube BJ, Engrav LH, Marvin JA, Heimbach DM. Determinants of donor site infections in small burn grafts. *J Burn Care Rehabil* 1989;10:531–5.